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MARY E. BAK
HOWSON AND HOWSON, SPRING HOUSE CORPORATE CENTER
BOX 457
SPRING HOUSE, PA 19477

EXAMINER	
GIBBS, TERRA C	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,369	BORCHERS ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Election mailed on May 7, 2004.

Claims 1-20 are pending in the instant application. Claims 15-18 and SEQ ID NOs: 10, 11, 12, 14-19, 21-36, 39, 40, 41, 46, 48-60, 63, 65, 66-75, 77-84, 86, and 87 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on May 7, 2004.

Claims 1-14, 19, and 20 have been examined on the merits.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-14, 19, and 20) is acknowledged. It is noted that Applicants were also required to elect one (1) antisense oligonucleotide from claim 3. Applicant's election with traverse of SEQ ID NO:37 is acknowledged. It is noted that in a telephone interview with Mary Bak, on June 28, 2004, the Examiner was informed that the election made on May 7, 2004 contained a typographical error. The election of one (1) antisense oligonucleotide from claim 3 should have been SEQ ID NO:47, instead of SEQ ID NO:37, as indicated in the election made May 7, 2004. The Examiner has acknowledged this typographical error and SEQ ID NO:47, not SEQ ID NO:37 will be examined with the elected invention.

The election with traverse of SEQ ID NO:47 is acknowledged. The traversal is three-fold. First, Applicants argue that such a narrow restriction requirement effectively deprives Applicants of the right to obtain patent protection on a reasonable scope of the invention.

Applicants contend that in order to cover the full scope of his invention, 79 different applications would need to be filed, which is unreasonable. Second, Applicants argue that the restriction requirement of claim 3 should more properly be a species election. Applicants contend that the antisense compounds of the present invention each target and modulate the expression of the same gene and each target is a species of the genus composed of sequences found within SEQ ID NO:3. Finally, Applicants argue that the restriction to a single sequence contravenes the policies of the Commissioner. Applicants contend that it has been determined that normally up to ten sequences are deemed to constitute a reasonable number of sequences for examination purposes.

Applicant's arguments have been fully considered but are not found persuasive because of the reasons set forth in the previous Restriction Requirement mailed April 2, 2004. For example, the instant antisense sequences are considered to be unrelated, since each antisense sequence claimed is structurally and functionally independent and distinct for the following reasons: each antisense sequence has a unique nucleotide sequence, each antisense sequence targets a different and specific region of ABC transporter MHC1, and each antisense, upon binding to ABC transporter MHC1, functionally modulates (increases or decreases) the expression of the gene and to varying degree (per applicants' Table 1 in the specification). Furthermore, a search of more than one (1) of the antisense sequences claimed in claim 3 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences. Regarding Applicants argument that the restriction requirement of claim 3 should more properly be a species election, the previous Restriction Requirement was not an election of species because the instant antisense sequences are considered to be distinct and independent inventions:

unique and structurally distinct nucleotide sequences. Regarding Applicants argument that it has been determined that normally up to ten sequences are deemed to constitute a reasonable number of sequences for examination purposes, see MPEP 808.02 where it states:

> Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05(c) - 806.05(i), the Examiner, in order to establish reasons for insisting upon restriction, must be shown by appropriate explanation of one of the following:
>
> (c) A different field of search: Where it is necessary to search for one of the distinct subjects in places where no pertinent art to the other subject exists, a different field of search is shown, even though the two are classified together.

It is noted that a search of the available sequence databases produces a listing of references disclosing the sequence most similar to the query sequence (target region). This is the "place" where the Examiner searches for prior art. The prior art relating to another query sequence (a different target region) will not be found in this "place"- a different listing of references must be generated and searched by the Examiner. Thus, a different search is shown, and restriction is proper.

In a telephone conversation with Attorney Mary Bak on July 21, 2004, the Examiner informed the Attorney that the instant application would be examined under linking claim practice. See MPEP 809.03. The Examiner informed the Attorney that Claim 1 links patentably distinct inventions of Groups I and II. The restriction between the linked inventions is subject to the nonallowance of the linking claim 1. Claim 1 will be examined with the elected invention. Upon the allowance of the linking claim(s), the restriction as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the

allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01. Attorney Mary Bak agreed to have the instant application examined under current PTO linking claim practice.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

The Information Disclosure Statements mailed December 17, 2001 and February 24, 2004 are acknowledged. The references referred to therein have been considered on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant claims read on a chemically modified compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding ABC transporter MHC 1, wherein said compound specifically hybridizes with and differentially inhibits the expression of one of the variants of ABC transporter MHC 1 relative to the remaining variants of ABC transporter MHC 1.

The claimed invention encompasses any nucleic acid compound that specifically hybridizes to any form of the ABC transporter MHC 1 gene, which includes sequences from mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology), and so forth. The specification as filed provides only a description of the human ABC transporter MHC 1 gene represented by SEQ ID NO. 3, ABC transporter MHC 1 –E (SEQ ID NO:88), ABC transporter MCH 1-C (SEQ ID NO:89, and ABC transporter MCH 1 –D (SEQ ID NO:90).

The specification provides only antisense compounds complementary to target sites, or "target nucleic acid" (see specification pages 10 and 11 lines 17-37 and 1-11, respectively) of the human ABC transporter MHC 1 mRNA molecule (SEQ ID NO:3), wherein such antisense compounds are effective to inhibit expression of the target sequence. Applicants have not provided any examples of antisense compounds complementary to target sites of the ABC transporter MHC 1 –E (SEQ ID NO:88), ABC transporter MCH 1-C (SEQ ID NO:89), or ABC transporter MCH 1 –D (SEQ ID NO:90), wherein such antisense compounds are effective to inhibit expression of the target sequence. Further the specification as filed, does not provide sufficient description that would allow one of skill in the art to use the antisense compounds complementary to target sites of the human ABC transporter MHC 1 mRNA molecule (SEQ ID

NO:3) to predict the structures of antisense compounds complementary to target sites or "target nucleic acid" of ABC transporter MHC 1 –E (SEQ ID NO:88), ABC transporter MCH 1-C (SEQ ID NO:89), or ABC transporter MCH 1 –D (SEQ ID NO:90). For example, which antisense targeted to ABC transporter MHC 1 mRNA molecule (SEQ ID NO:3) would also be inhibitory to SEQ ID NOs: 88, 89, and 90? The specification as filed does not provide any examples of an antisense targeted to ABC transporter MHC 1 mRNA molecule (SEQ ID NO:3) that would also inhibit gene expression of ABC transporter MHC 1 –E (SEQ ID NO:88), ABC transporter MCH 1-C (SEQ ID NO:89), or ABC transporter MCH 1 –D (SEQ ID NO:90).

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the

specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a sufficient number of representative species of compounds that target ABC transporter MHC 1-B, ABC transporter MHC 1-C, and ABC transporter MHC 1-E, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Claim Rejections - 35 USC § 112

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite because it is dependent on claim 1, drawn to a chemically modified antisense oligonucletoide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding ABC transporter MHC 1 (SEQ ID NO:3). It is unclear how claim 3, drawn to an antisense oligonucleotide comprising SEQ ID NO:47, where SEQ ID NO:47 is 20 nucleobases in length, can be an antisense oligonucletoide of any less than 20 nucleobases in length. Replacement with the language, "a chemically modified antisense oligonucletoide 20 to 50 nucleobases in length targeted to a nucleic acid molecule encoding ABC transporter MHC 1 (SEQ ID NO:3)", in claim 1 would overcome the instant rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-14, 19 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Watt et al. [U.S. Patent No. 6,566,135].

Claim 1 is drawn to a chemically modified compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding ABC transporter MHC 1 (SEQ ID NO:3), wherein said compound specifically hybridizes with and inhibits the expression of ABC transporter MHC 1, by at least 61%. Claims 2 and 4-14 are depend on claim 1 and include all the limitations of claim 1, with the further limitations, wherein the compound is an antisense oligonucletoide, wherein the antisense oligonucletoide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; wherein the compound comprises a pharmaceutically acceptable carrier or diluent and further comprises a colloidal dispersion system. Claim 19 is dependent on claim 1 and include all the limitations of claim 1, with the further limitations wherein said compound specifically hybridizes with and differentially inhibits the expression of one of the variants of ABC transporter MHC 1 relative to the remaining variants of ABC transporter MHC 1. Claim 20 is dependent on claim 1 and include all the limitations of claim 1, with the further limitations, wherein said compound hybridizes with and specifically inhibits the expression of a variant of ABC transporter MHC 1, wherein said variant is selected from the group consisting of ABC transporter MHC 1, ABC transporter MHC 1-B, ABC transporter MHC 1-C, and ABC transporter MHC 1-E.

Watt et al. disclose an antisense oligonucleotide targeted to the caspase 6 gene with the following sequence: 5'- ccggtgtcct agccctgagg-3' (see Watt et al. SEQ ID NO:159). The antisense oligonucleotide disclosed by Watt et al. is further modified to include an internucleoside linkage, a modified sugar moiety, a modified nucleobase or a chimeric oligonucleotide (see Watt et al. columns 7-10). This antisense oligonucleotide is reverse complementary to bases 1885-1903 of SEQ ID NO:3 of the instant invention. It is noted that the reverse complimentarity between the antisense oligonucleotide targeted to caspase 6 disclosed by Watt et al. and nucleobases 1885-1903 of SEQ ID NO:3 is not contiguous. However, the antisense oligonucleotide targeted to caspase 6 disclosed by Watt et al. exhibits almost 90% local similarity to nucleobases 1885-1903 of SEQ ID NO:3 of the instant invention, as it contains only two mismatches (see attached sequence alignment). Given this high degree of similarity, the antisense oligonucleotide targeted to Caspase 6 disclosed by Watt et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" since the instant specification at page 15, lines 11-15 teaches, "it is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable." Accordingly, the antisense oligonucleotide disclosed by Watt et al. would specifically hybridize to ABC transporter MHC 1 (SEQ ID NO:3) as claimed.

Regarding Applicants claim of a chemically modified compound that inhibits the expression of ABC transporter MHC 1, wherein the compound inhibits expression by at least 61%, the burden of establishing whether the prior art oligonucleotide has the further function of inhibiting the gene expression of at least 61% under generally any assay condition as claimed falls to applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977):

"Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicants to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is bases on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an Applicants to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore it falls to Applicant to determine and provide evidence that the oligonucleotide disclosed by Watt et al. would or would not have the additional "functional limitation" of "inhibiting expression" of ABC transporter MHC 1 gene by at least 61% under generally any assay conditions.

Further regarding Applicants claim of a chemically modified compound that inhibits the expression of ABC transporter MHC 1, wherein the compound specifically hybridizes with and differentially inhibits the expression of one of the variants of ABC transporter MHC 1 relative to the remaining variants of ABC transporter MHC 1, as recited in claim 19, or wherein the compound specifically hybridizes with and inhibits the expression of a variant of ABC transporter MHC 1, wherein said variant is selected from the group consisting of ABC transporter MHC 1, ABC transporter MHC 1-B, ABC transporter MHC 1-C, ABC transporter MHC 1-D, and ABC transporter 1-E, as recited in claim 20, the burden of establishing whether the prior art oligonucleotide has the further function of specifically hybridizes with and

differentially inhibits the expression of one of the variants of ABC transporter MHC 1 relative to the remaining variants of ABC transporter MHC 1, as recited in claim 19, or specifically hybridizes with and inhibits the expression of a variant of ABC transporter MHC 1, wherein said variant is selected from the group consisting of ABC transporter MHC 1, ABC transporter MHC 1-B, ABC transporter MHC 1-C, ABC transporter MHC 1-D, and ABC transporter 1-E, as recited in claim 20, falls to applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as described above.

Therefore, absent evidence to the contrary, claims 1, 2, 4-14, 19 and 20 are anticipated by Watt et al.

Claims 1, 2, 4, 5, 11, 12, 13, 14, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al. (Journal of Immunotherapeutics, 1998 Vol. 21:32-40) [Applicants reference AY].

Claims 1, 2, 4, 5, 11, 12, 13, 14, 19, and 20 are described above in the 35 U.S.C. 102(e) rejection against claims 1, 2, 4-14, 19 and 20 as being anticipated by Watt et al. [U.S. Patent No. 6,566,135].

The instant specification at page 8, lines 1-10 discloses, "three phosphorothioate antisense oligonucleotides, 22 to 27 nucleotides in length, targeted to nucleotides 46 to 25, 1428 to 1402, and 2214 to 2188 (where numbering starts at the initiation codon) were tested, and the most pronounced effect on inhibition of TAP function and downregulation of MHC class I molecule expression at the cell surface was observed with the antisense oligonucleotide targeted near the translational start site of ABC translocator, MHC 1".

Regarding Applicants claim of a chemically modified compound that inhibits the expression of ABC transporter MHC 1, wherein the compound inhibits expression by at least 61%, the burden of establishing whether the prior art oligonucleotide has the further function of inhibiting the gene expression of at least 61% under generally any assay condition as claimed falls to applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicants to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is bases on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an Applicants to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore it falls to Applicant to determine and provide evidence that the oligonucleotide disclosed by Wong et al. would or would not have the additional "functional limitation" of "inhibiting expression" of ABC transporter MHC 1 gene by at least 61% under generally any assay conditions.

Further regarding Applicants claim of a chemically modified compound that inhibits the expression of ABC transporter MHC 1, wherein the compound specifically hybridizes with and differentially inhibits the expression of one of the variants of ABC transporter MHC 1 relative to the remaining variants of ABC transporter MHC 1, as recited in claim 19, or wherein the

compound specifically hybridizes with and inhibits the expression of a variant of ABC transporter MHC 1, wherein said variant is selected from the group consisting of ABC transporter MHC 1, ABC transporter MHC 1-B, ABC transporter MHC 1-C, ABC transporter MHC 1-D, and ABC transporter 1-E, as recited in claim 20, the burden of establishing whether the prior art oligonucleotide has the further function of specifically hybridizes with and differentially inhibits the expression of one of the variants of ABC transporter MHC 1 relative to the remaining variants of ABC transporter MHC 1, as recited in claim 19, or specifically hybridizes with and inhibits the expression of a variant of ABC transporter MHC 1, wherein said variant is selected from the group consisting of ABC transporter MHC 1, ABC transporter MHC 1-B, ABC transporter MHC 1-C, ABC transporter MHC 1-D, and ABC transporter 1-E, as recited in claim 20, falls to applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as described above.

Therefore, absent evidence to the contrary, claims 1, 2, 4, 5, 11, 12, 13, 14, 19, and 20 are anticipated by Wong et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, and 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jackson et al. (Proc. Natl. Acad. Sci., 1993 Vol. 90:11079-11083) in view Wong et al. (Journal of Immunotherapeutics, 1998 Vol. 21:32-40) [Applicants reference AY], and Baracchini et al. (U.S. Patent No. 5,801,154).

Claim 1 is drawn to a chemically modified compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding ABC transporter MHC 1 (SEQ ID NO:3), wherein said compound specifically hybridizes with and inhibits the expression of ABC transporter MHC 1, by at least 61%. Claims 2 and 4-14 are dependent on claim 1 and include all the limitations of claim 1, with the further limitation wherein the compound is an antisense oligonucleotide; wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising an antisense oligonucleotide 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding ABC transporter MHC 1 (SEQ ID NO:3) and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Jackson et al. teaches the full-length sequence of human ABC transporter MHC 1 as represented in SEQ ID NO:3 of the instant invention (see Jackson et al., Figure 1). Jackson et al. do not teach antisense targeted to ABC transporter MHC 1, including antisense with a length of 8 to 50 nucleobases. Jackson et al. also do not teach antisense targeted to a nucleic acid encoding ABC transporter MHC 1, wherein the antisense comprises modified internucleoside linkages, or wherein the antisense is a chimeric antisense molecule.

Wong et al. suggest making ABC transporter MHC 1 inhibitors, including antisense nucleic acids of ABC transporter MHC 1 (see Abstract). Wong et al. also teach antisense targeted to ABC transporter MHC 1, including antisense with a length of 8 to 50 nucleobases, and phosphorothioate modifications (see page 34, first column at Oligonucleotides). Wong et al. do not teach antisense targeted to a nucleic acid encoding ABC transporter MHC 1 wherein the antisense comprises modified sugar moieties, and wherein the antisense is a chimeric antisense molecule.

Baracchini et al. teach modified antisense oligonucleotides, including 2'-O'methoxyethyl sugar modifications, 5-methylcytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity (see for example columns 6-9). Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

It would have been obvious to one of ordinary skill in the art to make an antisense oligonucletoide targeted to a nucleic acid encoding ABC transporter MHC 1 using the sequence taught by Jackson and the motivation of Wong et al. It would have been obvious to make a

length within the range of 8 to 50 nucleobases (as taught by Wong et al. and Baracchini et al.) because antisense of a short length are more easily synthesized and easier to deliver to cells. It would have been further obvious to make said antisense comprising modifications, including 2'-O'methoxyethyl sugar modifications, 5-methylcytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, as taught by Baracchini et al., because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule, (see for example, Baracchini et al. column 6, paragraph 3).

It would have been obvious to one of ordinary skill in the art to make an antisense compound comprising antisense targeted to ABC transporter MHC 1 and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al. Further, it would have been obvious to make an antisense compound targeted to ABC transporter MHC 1 because Wong et al. teach generally making inhibitors to ABC transporter MHC 1, and teach the specific embodiment of antisense nucleic acids, and Jackson et al. taught a human ABC transporter MHC 1 encoded by a nucleic acid comprising ABC transporter MHC 1 of the instant invention.

One skilled in the art would have been motivated to make an antisense molecule targeted to a nucleic acid encoding ABC transporter MHC 1 because Wong et al. explicitly teaches inhibiting the expression of ABC transporter MHC 1 using antisense nucleic acids and it is well known in the art that antisense is a means by which a target protein can be specifically targeted

for functional studies and Jackson et al. teach human ABC transporter MHC 1 as a protein to be studied and teach the full length sequence of a nucleic acid encoding human ABC transporter MHC 1. One of ordinary skill in the art would be motivated to make such antisense of a length within the range of 8 to 50 nucleotides for ease of synthesis and delivery and because it is conventional in the art to make antisense within this size range (as exemplified by Wong et al. and Baracchini et al.). One of ordinary sill would have been motivated to incorporate the modifications taught by Baracchini et al. into an antisense molecule targeted to ABC transporter MHC 1, for the benefits of stability and improved hybridization.

Therefore, the invention of claims 1, 2, and 5-18 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Conclusion

A chemically modified compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding ABC transporter MHC 1 (SEQ ID NO:3), wherein said compound specifically hybridizes with and inhibits the expression of ABC transporter MHC 1, by at least 61%, wherein the compound is an antisense oligonucleotide, wherein the antisense oligonucleotide has a sequence comprising SEQ ID NO:47 is free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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tcg
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JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600